

EXHIBIT F



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/302,287	06/11/2014	Stuart William REID	O0366.70004US02	6959

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EXAMINER

ROSENWALD, STEVEN ERIC

ART UNIT	PAPER NUMBER
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1759

NOTIFICATION DATE	DELIVERY MODE
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08/16/2016

ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Patents_eOfficeAction@WolfGreenfield.com
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Office Action SummaryApplication No.
14/302,287Applicant(s)
REID ET AL.Examiner
STEVEN E. ROSENWALDArt Unit
1759AIA (First Inventor to File)
Status
No**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --****Period for Reply**A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 July 2016.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
- 4) ☒ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

- 5) ☒ Claim(s) 71-105 is/are pending in the application.
5a) Of the above claim(s) 71-90 is/are withdrawn from consideration.
- 6) ☐ Claim(s) _____ is/are allowed.
- 7) ☒ Claim(s) 91-105 is/are rejected.
- 8) ☐ Claim(s) _____ is/are objected to.
- 9) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

- 10) ☒ The specification is objected to by the Examiner.
- 11) ☒ The drawing(s) filed on 06/11/2014 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

- a) ☐ All b) ☐ Some** c) ☐ None of the:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)
Paper No(s)/Mail Date See Continuation Sheet.
- 3) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 4) ☒ Other: See Continuation Sheet.

Continuation Sheet (PTOL-326)

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Continuation of Attachment(s) 2). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :07/18/2014, 03/24/2015, 07/26/2016.

Continuation of Attachment(s) 4). Other: Third party submission IDS 05/19/2016.

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DETAILED ACTION

The present application is being examined under the pre-AIA first to invent provisions.

Election/Restrictions

Claims 72-90 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 26 July 2016.

Priority

This application repeats a substantial portion of prior Application No. 12/339,956, filed 19 December 2008, and adds disclosure not presented in the prior application (a plurality of individually addressable nanopores). Because this application names the inventor or at least one joint inventor named in the prior application, it may constitute a continuation-in-part of the prior application. Should applicant desire to claim the benefit of the filing date of the prior application, attention is directed to 35 U.S.C. 120, 37 CFR 1.78, and MPEP § 211 *et seq.*

The priority date for the limitation “a plurality of individually addressable nanopores” is considered to be the filing date of this application, 11 June 2014.

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Drawings

The drawings are objected to under 37 CFR 1.83(a). The drawings must show every feature of the invention specified in the claims. Therefore, the individually addressable nanopores must be shown or the feature(s) canceled from the claim(s). No new matter should be entered.

Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as “amended.” If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either “Replacement Sheet” or “New Sheet” pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

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Specification

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: The arrangement and structure of the plurality of individually addressable nanopores is not described in the specification.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of 35 U.S.C. 112(b):

(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 95 and 97 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

1. Claims 95 and 97 recite "resistance is measured", making it unclear what structure is being recited. In addition, this limitation is considered to be a method step in a claim to a device.

A single claim which claims both an apparatus and the method steps of using the apparatus is indefinite under 35 U.S.C. 112(b) or pre-AIA 35 U.S.C. 112, second paragraph. See MPEP 2173.05(p).

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Claim Rejections - 35 USC § 102

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 91-95, 98-103 and 105 are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Chen *et al.* (US 2011/0287414 A1).

Regarding claim 91, Chen teaches a system for nucleic acid sequencing (Abstract, pars. [0022], [0024]), comprising: (a) a chip (par. [0043], Figs. 3A-1 to 3B, 300 of Fig. 3A-1) comprising a plurality of individually addressable nanopores (100/302), an individually addressable nanopore of said plurality of individually addressable nanopores containing at least one nanopore formed in a membrane disposed adjacent to an electrode (118a/b), wherein each individually addressable nanopore is adapted to aid in the detection of said nucleic acid molecule or a portion (pars. [0022] to [0024]); and (b) a processor coupled to said chip (306, pars. [0014], [0032], [0043]), wherein said processor is programmed to aid in characterizing a nucleic acid sequence of said nucleic acid molecule based on electrical signals received from said plurality of individually addressable nanopores (*Ibid.*).

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Regarding claim 92, Chen teaches said electrode is adapted to supply an electrical stimulus across said membrane, which stimulus enables the generation of a detectable signal upon molecular flow of said nucleic acid molecule or portion thereof (par. [0032], for example).

Regarding claim 93, Chen teaches said membrane has a capacitance of greater than about $5\text{fF}/\mu\text{m}^2$ as measured across said membrane (par. [0028]).

Regarding claim 94, Chen teaches said membrane has a resistance greater than or equal to about $500\text{ M}\Omega$ as measured across said membrane (par. [0049], $10\text{ G}\Omega$).

Regarding claim 95, Chen teaches said resistance is measured with the aid of opposing electrodes disposed adjacent to said membrane (118a/b).

Regarding claim 98, Chen teaches each individually addressable nanopore is adapted to regulate molecular flow (pars. [0016] to [0018]; “draw the molecule from a surrounding fluid into the nanopore”, “allows the molecule to progress through the nanopore”).

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Regarding claim 99, Chen teaches each individually addressable nanopore is adapted to regulate molecular flow with the aid of an electrical stimulus applied to said nanopore (pars. [0016] to [0018]; “electrical stimulus”).

Regarding claim 100, Chen teaches said electrical stimulus comprises one or more voltage pulses (pars. [0021], [0039]).

Regarding claim 101, Chen teaches each individually addressable nanopore is adapted to regulate molecular flow adjacent to said at least one nanopore (pars. [0016] to [0018]; “draw the molecule from a surrounding fluid into the nanopore”, “allows the molecule to progress through the nanopore”).

Regarding claim 102, Chen teaches each individually addressable nanopore is adapted to regulate molecular flow through said at least one nanopore (pars. [0016] to [0018]; “draw the molecule from a surrounding fluid into the nanopore”, “allows the molecule to progress through the nanopore”).

Regarding claim 103, Chen teaches each individually addressable nanopore is adapted to detect said nucleic acid molecule or a portion thereof upon molecular flow of said nucleic acid molecule or portion thereof through or adjacent to said at least one nanopore (par. [0017]; “recording of useful electrical signature(s) of the molecule for characterization”).

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Regarding claim 105, Chen teaches said electrode is coupled to an integrated circuit that processes a signal detected with the aid of said electrode (par. 0032]; circuit 122 of Fig. 3B).

Claim Rejections - 35 USC § 102/103

The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under pre-AIA 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under pre-AIA 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

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under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of pre-AIA 35 U.S.C. 103(c) and potential pre-AIA 35 U.S.C. 102(e), (f) or (g) prior art under pre-AIA 35 U.S.C. 103(a).

3. Claims 96-97 and 104 are rejected under pre-AIA 35 U.S.C. 102 (b) as anticipated by or, in the alternative, under pre-AIA 35 U.S.C. 103(a) as obvious over Chen *et al.* (US 2011/0287414 A1).

Regarding claim 96, Chen teaches the membrane has a resistance of 10 G Ω (par. [0049]), which is an order of magnitude larger than less than or equal to about 1 G Ω as recited in claim 96.

The second full paragraph of applicant's specification page 28 teaches the "lipids typically comprise a head group, an interfacial moiety and two hydrophobic tail groups which may be the same or different. Suitable head groups include, but are not limited to, neutral head groups, such as diacylglycerides (DG) and ceramides (CM); zwitterionic head groups, such as phosphatidylcholine (PC)." This membrane is then treated to insert an α -hemolysin, specification page 42, example 1. Chen teaches "a alpha hemolysin (α HL) nanopore device having a single .alpha.HL protein 108 embedded in a diphytanoylphosphatidylcholine (DPhPC) lipid bilayer" in par. [0035], where "di" reads on two hydrophobic tail groups.

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Chen teaches all structure recited in claims 91 and 94. Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). MPEP 2112.01.

Since Chen's membrane is substantially identical to the claimed membrane, Chen's membrane is inherently capable of the recited resistance.

In addition, Chen teaches that resistance is measured in order to determine the structural integrity of a lipid bilayer, and that higher voltages (e.g. $\sim 2V$) leads to destruction of the bilayer (par. [0049]). Resistance is controlled by Ohm's law; $V = iR$, where V is voltage, i is current, and R is resistance. In other words, resistance is directly proportional to voltage. Since Chen teaches all structure recited in claims 91 and 94, it would have been obvious to a person having ordinary skill in the art at the time the invention was made (filed) to reduce the applied voltage to avoid destruction of the lipid bilayer, which would lead to a resistance of less than or equal to about $1\text{ G}\Omega$ according to Ohm's law, with a reasonable expectation of success in detection of lipid bilayer integrity.

Regarding claim 97, Chen teaches said resistance is measured with the aid of opposing electrodes disposed adjacent to said membrane (118a/b).

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Regarding claim 104, Chen teaches said processor is in a workstation that is in proximity to said chip (par. [0032], processor 124 in in proximity to the chip, and although not shown in Fig. 3B it is obviously connected at the BUS in the lower right of the more complex device of Fig. 3B).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEVEN E. ROSENWALD whose telephone number is (571)270-1149. The examiner can normally be reached on M-F, 9A to 5:30P.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Luan Van can be reached on (571)272-8521. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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/S. E. R./

Examiner, Art Unit 1759

/LUAN VAN/

Supervisory Patent Examiner, Art Unit 1759